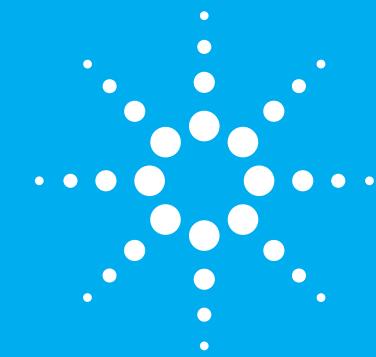




Analytical Instrument  
Qualification and  
System Validation



USP <1058>  
21 CFR Part 11  
GxPcGMP  
PIC/S SOP  
ISO 17025  
QA/QC  
GLP DQ  
ICH IQ  
FDA 00  
OECD PQ  
GCP

Agilent Technologies

Analytical Instrument Qualification and System Validation

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# **Analytical Instrument Qualification and System Validation**

**Ludwig Huber**

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## Table of Content

<b>Preface</b> .....	<b>III</b>
<b>1      Introduction</b> .....	<b>1</b>
1.1    Literature Overview .....	3
1.2    Terminology: Validation vs. Qualification .....	5
1.3    Components of Analytical Data Quality .....	6
<b>2      Regulations and Quality Standards</b> .....	<b>9</b>
2.1    Good Laboratory Practice Regulations .....	10
2.2    Current Good Manufacturing Practice Regulations .....	11
2.3    International Conference for Harmonization .....	13
2.4    Pharmaceutical Inspection Convention Scheme (PIC/S) .....	14
2.5    ISO/IEC 17025 .....	15
2.6    21 CFR Part 11 – FDA's Regulation on Electronic Records and Signatures .....	15
2.7    Learning from Regulations and Quality Standards .....	16
<b>3      Qualification of Analytical Instruments</b> .....	<b>17</b>
3.1    Qualification Planning .....	19
3.2    Design Qualification .....	22
Specifications .....	23
Vendor Assessment .....	25
3.3    Installation Qualification .....	26
Testing for Installation Qualification .....	29
3.4    Operational Qualification (OQ) .....	30
3.5    Performance Qualification .....	32
(Preventive) Maintenance and Repair .....	34
Change control .....	35

---

<b>4 Validation of Software and Computer Systems .....</b>	<b>37</b>
4.1 Master and Project Planning .....	39
4.2 Requirement Specifications .....	40
4.3 Vendor Assessment .....	41
4.4 Installation Qualification.....	43
4.5 Operational Qualification .....	44
4.6 Performance Qualification .....	47
4.7 Configuration Management and Change Control .....	47
4.8 Validation Report .....	49
4.9 Validation of Existing/legacy Systems .....	49
4.10 Validation of Spreadsheet Applications .....	50
<b>5 Implementing USP Chapter &lt;1058&gt; .....</b>	<b>51</b>
5.1 <1058> Instrument Groups .....	52
5.2 Allocating Instrument into Instrument Groups .....	54
5.3 Procedures and Qualification Protocols for Three Groups .....	54
5.4 Responsibilities, Communication and Training .....	56
Users .....	56
Quality Assurance.....	57
Developers, Manufacturers and Vendors.....	57
<b>Agilent Technologies' Commitment to Compliance .....</b>	<b>58</b>
<b>References .....</b>	<b>59</b>
<b>Glossary.....</b>	<b>61</b>

## Preface

### Good to know!

Qualification of analytical instruments is required by regulations and quality standards.

Qualification of analytical instruments and validation of systems is required by many national and international regulations, quality standards such as ISO 17025 and company policies. If executed correctly, it also helps to improve instrument uptime and to avoid out-of-specification situations (OOS) in laboratories. This "Analytical Instrument Qualification" primer guides analysts, laboratory managers, quality assurance managers and validation professionals through instrument and system validation at minimal extra cost.

The concept, examples, templates and recommended procedures are based on my more than 20 years of multinational experience and incorporate knowledge from validation and qualification practices applied at Agilent Technologies and Labcompliance. Readers of this book will learn how to speed up their validation and qualification process, thereby avoiding troublesome reworking and gaining confidence for audits and inspections.

Due to limited space, I could not include all the information that is available and of interest to readers. For additional information, I can refer you to three text books:

- 1) *P. Coombes, Laboratory Systems Validation Testing and Practice, DHI Publishing, LTD, Raleigh, USA 2002*
- 2) *C.C.Chan, H. Lam, Y.C.Lee, X.M. Zhang, Analytical Method Validation and Instrument Performance Verification., Wiley Interscience, Hoboken USA, 2004*
- 3) *L. Huber, Validation and Qualification in Analytical Laboratories, Interpharm, Informa Healthcare, New York, USA, 1998, Second revision 2007*

Some text information and figures in this primer have been taken from 2) and 3) with permission from the publishers.

The concepts and ideas expressed in this primer are my own and do not necessarily reflect official Agilent or Labcompliance policies. Regulatory requirements and inspection and enforcement practices are quite dynamic. What is appropriate today may not be appropriate tomorrow.

Requirements in some areas may go up, in others down. Regulations don't change quickly but guidelines and especially inspection practices can.

A timely update of all information is important and only possible using on-line information tools, such as the Internet. To take this fact into account, I recommend a couple of websites with regular updates related to compliance in general and specifically for laboratories:

**<http://www.fda.gov>**

This is the primary resource for FDA compliance directly from the United States Food and Drug Administration.

**<http://www.agilent.com/chem/pharmaqaqc>**

The Agilent website for pharmaceutical QA/QC analysis with monthly newsletter for regular updates.

**<http://www.labcompliance.com>**

A website with regular updates including tutorials and many references related to all compliance issues in laboratories.

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# Chapter 1

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## Introduction

## Introduction

### Good to know!

Equipment shall be routinely calibrated, inspected and checked according to a written program to ensure proper performance (US FDA 21 CFR 211).

The objective of any chemical analytical measurement is to get consistent, reliable and accurate data. Proper functioning and performance of analytical instruments and computer systems plays a major role in achieving this goal. Therefore, analytical instrument qualification (AIQ) and computer system validation (CSV) should be part of any good analytical practice. There is a second aspect to why validation and qualification are important, and this is equally important for those working in a regulated and in an accredited environment. Even though frequently not directly spelled out in regulations and official guidelines, such as Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP), or in quality standards, such as the International Organization for Standardization (ISO) Standard 17025, validation and qualification is usually required. This is confirmed by typical statements such as this one that appears in the U.S. cGMP (current Good Manufacturing Practice) regulations<sup>1</sup>: "Equipment shall be routinely calibrated, inspected and checked according to a written program to ensure proper performance" or by the more general requirement "Equipment should be suitable for its intended use". Although there were lots of discussions about the approach for qualification of analytical instruments in the 90's and in the early years of this century, this has changed since the USP has published the final version of the chapter <1058> entitled Analytical Instrument Qualification.<sup>2</sup>

Following a literature and regulatory overview, this primer will provide information on the entire qualification and validation process from planning, writing specifications as well as vendor qualification to installation, initial and on-going operation.

It covers:

- Literature overview with milestones on instrument qualification and system validation in laboratories.
- Overview on regulations and quality standards with impact on analytical instrument qualification.
- Qualification of equipment hardware, for example, a spectrometer or liquid chromatograph.
- Validation of analytical computerized systems.
- Implementing USP chapter <1058>.

Special focus is placed on getting a good understanding of and implementing USP chapter <1058>. After an introduction to the chapter's approach for instrument qualification, this primer will lead you through individual qualification phases and give recommendations for implementation.

The primer will not only help readers understand the instrument qualification process, but also offers templates and examples to easily implement qualification. Because of the nature and size of this primer, all the details of operational qualification and system validation cannot be given. For more details, please refer to reference articles and text books<sup>3-5</sup>.

Exact procedures and test parameters very much depend on the type of instrument and applications. Details on recommendations and services can be obtained from instrument vendors. Although the primer has recommendations for validation of standard commercial computerized analytical systems without the need for major customization, it does not give details on validation of complex systems, such as Laboratory Information Management Systems (LIMS), or on validation activities during software development but refers to further literature<sup>7-11</sup>.

## 1.1 Literature Overview

### Good to know!

FDA guidelines, publications from industry task forces and reference books help to implement analytical instrument qualification.

Due to their importance, equipment qualification issues have been addressed by several organizations. Before 1990 the regulatory focus of instrument and computer validation was primarily on manufacturing equipment, which changed after 1990. In response to industry task forces, regulatory agencies published guidance documents that helped the industry to better understand regulatory requirements. In addition, private authors published reference books with practical recommendations for implementation:

- The Pharmaceutical Analysis Science Group (UK) developed a position paper on the qualification of analytical equipment<sup>6</sup>. This paper was a benchmark because it introduced the 4Q model with design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ) for analytical equipment qualification.
- The Laboratory of the Government Chemist (LGC) and Eurachem-UK, developed a guidance document with definitions and step-by-step instructions for equipment qualification<sup>3</sup>.

- The United States Food and Drug Administration developed principles of software validation<sup>7</sup>.
- The Good Automated Manufacturing Practices Forum (GAMP) developed guidelines for computer validation in 2001<sup>8</sup> and in 2008<sup>9</sup>. These guides have been specifically developed for computer systems in general, and because of their importance have also been used for validation of laboratory systems.
- GAMP also published a Good Practice Guide for Validation of Laboratory Systems<sup>10</sup>. It recommends validation activities and procedures for seven different instrument categories.
- Huber authored two validation reference books for the analytical laboratory<sup>5, 11</sup>. The first one covers all validation aspects of an analytical laboratory including equipment, analytical methods, reference compounds and people qualification. The second one covers the validation of computerized and networked systems in analytical laboratories.
- The Parenteral Drug Association (PDA) developed a technical paper on the validation of laboratory data acquisition system<sup>12</sup>.
- Coombes authored a book on laboratory systems validation testing and practice<sup>4</sup>. The term laboratory systems validation (LSV) was used to make a distinction from computer system validation (LSV) and equipment qualification (EQ).
- Chan and colleagues published the book Analytical Method Validation and Instrument Performance Verification<sup>13</sup>. This book has several chapters with practical recommendations for instrument qualification.

### Good to know!

Qualification of equipment and validation of computer systems are not one time events. They start with the definition of the product or project and end with system retirement.

### All these guidelines and publications follow a couple of principles:

- Qualification of equipment and validation of computer systems are not one time events. They start with the definition of the product or project and setting user requirement specifications and cover the vendor selection process, installation, initial operation, ongoing use and change control.

- All publications refer to some kind of life cycle model with a formal change control procedure being an important part of the whole process.

### Good to know!

The 4Q model is recommended for users of commercial instruments without significant customization by the user.

Different models have been suggested for different kinds of instruments. For example, the 4Q model as described by Freeman<sup>6</sup> and Bedson<sup>3</sup> has been recommended for users of commercial instruments without significant customization by the user. The V-model as recommended by GAMP4<sup>8</sup> is suitable for software development as well as for users of commercial instruments with customization by the user.

A major breakthrough came when USP released its general chapter on analytical instrument qualification<sup>2</sup>. The major benefit of the chapter was that it formalized the 4Q model and clarified some issues that have been frequently discussed before, for example, that an instrument's firmware does not need separate qualification, but should be qualified as part of the instrument hardware.

## 1.2 Terminology: Validation vs. Qualification

An agreement on terminology is of utmost importance for a common understanding of validation and qualification. The author has frequently noted at validation symposia that different speakers used different terms for the same thing and the same terms for different things. Most frequent question arose about the words validation and qualification. USP has recognized this and addressed it in a paragraph on the first page of chapter <1058>. The word qualification relates to instruments that can be individual modules and also systems, for example, a complete HPLC system comprised of a sampling system, a pump, a column compartment and a detector. Checking the baseline noise of a detector and comparing the results with previously defined specifications would be an example for qualification. Qualification is done independently from a specific application or sample. Typically the type of specifications can be found in the vendor's product specification sheet.

The word validation relates to applications, processes and methods. For example, for method validation we specify the limit of quantitation or limit of detection of our sample compounds. Such specifications can only be verified with a complete system and accessories such as the

right chromatographic column, calibration standards and SOPs for running the test.

Unfortunately, validation and qualification are frequently used interchangeably. For example, for software and computer systems the term validation is always used, even though according to the previous definition qualification should be used. Therefore, in the context of software and computer systems, this primer will also use the term validation.

The FDA and other agencies do not really care what users call it, validation or qualification. The inspector's question will always be: how did you make sure that the data are accurate. As long as there is a good answer, for example through validation of systems and methods, it is of secondary importance how users call it. However, agreement on terminology is of utmost importance within a company, so that everybody has the same understanding of qualification and validation. Therefore, terminology and the exact meaning should be documented in a glossary.

### 1.3 Components of Analytical Data Quality

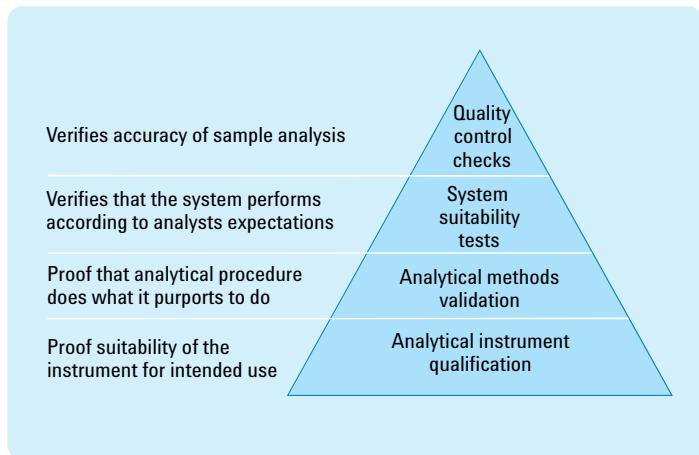
#### Good to know!

Whether you validate methods, verify the suitability of a system or analyze quality control samples, you should always have qualified the instrument first.

There were many discussions about the need for instrument qualification in analytical laboratories before the release of USP <1058>, taking into account that there are several other components of data quality, for example, method validation, system suitability testing and the analysis of quality control samples.

USP started the chapter by giving good reasons why instrument qualification is important. Figure 1 illustrates the different components of data quality with analytical instrument qualification as the foundation at the bottom.

Whether you validate methods or systems, verify the suitability of a system for its intended use or analyze quality control samples, you should always qualify the instrument first. It is the basis of all other components. It is the collection of documented evidence to demonstrate that an instrument suitably performs for its intended purpose and that it is properly maintained and calibrated. If the instrument is not well qualified, weeks can be spent to validate an HPLC method without success until a determination is made that the HPLC detector did not meet specifications for linearity or baseline noise.



**Figure 1**  
**Components of analytical data quality.**

After you have qualified the instrument, you validate analytical methods on qualified instruments. This should prove that the method works as intended. We do this independently of any specific instrument. If you want to use the method on instruments from different vendors, you also should validate the method on those instruments.

Then you can combine any specific instrument with a specific method and run system-suitability tests. This ensures that the complete system meets the analyst's expectations under the specific conditions of the tests.

The highest level of testing is the analysis of quality control samples. You analyze standards or samples with known amounts and compare the results with the correct amounts. Again a prerequisite to show that this works is to use qualified instruments and validated methods.



## Chapter 2

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### **Regulations and Quality Standards**

## Regulations and Quality Standards

Qualification of instruments and validation of systems is a requirement of the FDA and equivalent international regulations. No or inadequate qualification can cause regulatory actions, such as shipment stops of drugs and APIs. The rationale behind this is that analytical test results obtained with no or inadequately qualified instruments can be wrong. Because of the importance of compliance, we dedicate this chapter to regulations and quality standards. The purpose of the regulations and standards are listed together with key requirements.

Regulations are quite static and typically don't change for several years. More dynamic than regulations are inspection and enforcement practices. Information can be found in the FDA's inspection documents such as warning letters, establishment inspection reports (EIR) and 483 form inspectional observations. Highly important are FDA warning letters. They are sent to companies in case of serious regulatory violations. Companies are expected to respond within 15 days. If there is no response or if the response is inadequate, the FDA will take further actions which may cause delay of new product approvals, import alerts and denials, or product recalls. Since March 2003 warning letters are reviewed by higher-level FDA officials and reflect the FDA's current thinking. Warning letters are published on two FDA websites:

<http://www.fda.gov/cder/warn/index.htm> and  
<http://www.fda.gov/foi/warning.htm>.

The only problem is that there are thousands of them and they mostly relate to marketing and labeling, so it is difficult to find the ones that are of interest to laboratories. Interesting sites exist that only publish warning letters related to GxP issues. For example, <http://www.fdawarningletter.com> has many quotes related to the qualification of instruments and validation of computer systems.

### 2.1 Good Laboratory Practice Regulations

Good laboratory practice (GLP) regulations deal with the organization, processes and conditions under which preclinical laboratory studies are planned, performed, monitored, recorded and reported. GLP data are intended to promote the quality and validity of study data. GLP regulations were first proposed by the U.S. FDA in November 1976, and final regulations were coded as Part 58 of Chapter 21 of the Code of Federal Regulations in 1979<sup>15</sup>. The Organization for Economic Cooperation and

Development (OECD) published the principles of Good Laboratory Practice in the Testing of Chemicals in 1982<sup>16</sup>, which has been since updated<sup>17</sup> and incorporated by OECD member countries. In the meantime most industrial countries and some developing countries have their own GLPs.

All GLP regulations include chapters on equipment design, calibration and maintenance, for example, U.S. GLP regulations, Sections 58.61 and 58.63<sup>15</sup>:

- Automatic, mechanical, or electronic equipment used in the generation, measurement, or assessment of data shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.
- Equipment used for generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized.
- Written standard operating procedures shall set forth in sufficient detail the methods, materials, and schedules to be used in routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment and shall specify remedial action to be taken in the event of failure or malfunction of equipment.
- Written records shall be maintained on all inspection operations.

The GLP principles of the OECD include similar but shorter sections on equipment<sup>17</sup>:

- The apparatus used for the generation of data and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
- Apparatus and materials used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of procedures should be maintained.

## 2.2 Current Good Manufacturing Practice Regulations

Good Manufacturing Practice (GMP) regulates manufacturing and its associated quality control. GMP regulations have been developed to ensure that medicinal (pharmaceutical) products are consistently produced and controlled according to the quality standards appropriate to their intended use. In the United States, the regulations are called

Current Good Manufacturing Practices (CGMP) to account for the fact that the regulations are dynamic rather than static. They are defined in Title 21 of the U.S. Code of Federal Regulations, 21 CFR 210-*Current Good Manufacturing Practice for Drugs, General* and 21 CFR 211-*Current Good Manufacturing Practice for Finished Pharmaceuticals*<sup>1</sup>. Drugs marketed in the United States must first receive FDA approval and must be manufactured in accordance with the U.S. cGMP regulations. Because of this, FDA regulations have set an international regulation benchmark for pharmaceutical manufacturing.

In Europe, local GMP regulations exist in many countries. These are based on the EU directive: *Good Manufacturing Practice for Medicinal Products in the European Community*<sup>18</sup>. This EU GMP is necessary to permit free trade in medicinal products between the member countries. Regulations in the EU allow the marketing of a new drug in the member countries with the acquisition of just a single marketing approval. The intention of the EU GMP is to establish a minimum manufacturing standard for all member countries.

Like GLP, also all CGMP regulations include chapters on equipment design, calibration and maintenance, for example, U.S. CGMP regulation for pharmaceutical drugs, sections 211-140 b and 211-68<sup>1</sup>.

- Laboratory controls shall include the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.
- Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

### 2.3 International Conference for Harmonization

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industries in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

ICH publishes guidelines that are either signed into law by member countries, for example, in Europe or recommended as guidelines by national authorities, e.g., by the US FDA.

Examples for such guidelines are:

- Testing (Q1A)
- Validation of Analytical Procedures (Q2A, Q2B)
- Impurities in New Drug Substances (Q3A) and
- GMP Guide for Active Pharmaceutical Ingredients (Q7A) and
- Quality Risk Management (Q9)

One of the most important ICH documents is the GMP Guide for Active Pharmaceutical Ingredients<sup>19</sup>. Opposite to other official documents, Q7A has very specific requirements for equipment and computer systems in chapters 5.3 and 5.4:

- Equipment calibrations should be performed using standards traceable to certified standards, if existing.
- Records of these calibrations should be maintained.
- The current calibration status of critical equipment should be known and verifiable.
- Instruments that do not meet calibration criteria should not be used.
- Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact

## Good to know!

Installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks (ICH Q7A).

on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

- GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.
- Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

### 2.4 Pharmaceutical Inspection Convention Scheme (PIC/S)

PIC/S' mission is "to lead the international development, implementation and maintenance of harmonized Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products".

This is to be achieved by developing and promoting harmonized GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organizations. As of October 2008 there are 34 participating authorities in PIC/S and some more have applied for membership, for example the U.S. FDA.

The most relevant PIC/S document related to this primer is the Good Practice Guide: Using Computers in GxP Environments<sup>14</sup>. The guidance document is intended to provide a logical explanation of the basic requirements for the implementation, validation and operation of computerized systems. Recommendations are documented in chapters 4.6 and 4.8:

- Apart from user acceptance testing (OQ) versus the functional specification, the regulated user also has responsibility for the (PQ) performance qualification of the system.
- The validation documentation should cover all the steps of the life-cycle with appropriate methods for measurement and reporting, (e.g. assessment reports and details of quality and test measures), as required.

- Regulated users should be able to justify and defend their standards, protocols, acceptance criteria, procedures and records in the light of their own documented risk and complexity assessment.

## 2.5 ISO/IEC 17025

ISO/IEC 17025 is the most relevant ISO Standard for chemical laboratories<sup>20</sup>. It specifies the general requirements for the competence to carry out tests and/or calibrations. The standard is widely used as a quality system in environmental, food, chemical and clinical testing laboratories. It is used to assess laboratories that seek accreditation status.

### Good to know!

Equipment shall be calibrated or checked to establish that it meets the laboratory's specification requirements (ISO/IEC 17025).

The standard has many requirements related to the subject of this primer. The most important ones can be found in chapter 5.5.

- Calibration programs shall be established for key quantities or values of the instruments, where these properties have a significant effect on the results.
- Before being placed into service, equipment (including that used for sampling) shall be calibrated or checked to establish that it meets the laboratory's specification requirements and complies with the relevant standard specifications. It shall be checked and/or calibrated before use.
- Each item of equipment and its software used for testing and calibration and significant to the result shall, when practicable, be uniquely identified.
- Equipment that has been subjected to overloading or mishandling, gives suspect results, or has been shown to be defective or outside specified limits, shall be taken out of service.

## 2.6 21 CFR Part 11 – FDA's Regulation on Electronic Records and Signatures

In 1997 the United States Food and Drug Administration (FDA) issued a regulation that provides criteria for acceptance by the FDA of electronic records, electronic signatures and handwritten signatures<sup>21</sup>. With this regulation, entitled Rule 21 CFR Part 11, electronic records can be equivalent to paper records and handwritten signatures. The rule applies

to all industry segments regulated by the FDA that includes Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and current Good Manufacturing Practice (cGMP).

Part 11 requires computer systems used in FDA regulated environments to be validated. Chapter 10 (a) states:

- Computer systems should be validated to ensure accuracy, reliability and consistent intended performance.

There is no further instruction on how computer systems should be validated.

## 2.7 Learning from Regulations and Quality Standards

As we have seen in this chapter, all important regulations and ISO 17025 have one or more chapters on equipment and computers. The wording and the level of detail is different. For example, the words calibration and qualification are interchangeably used. Despite different terminology, the message is always the same: instruments and computer systems should be suitable for their intended use.

This means users should:

- Define the intended use, meaning write specifications.
- Formally assess the vendor's quality system.
- Formally document installation. ICH Q7A calls this installation qualification.
- Test the instrument in the user's environment for functional specifications. ICH and PIC/S call this operational qualification.
- Verify ongoing performance through ongoing preventive maintenance system tests.
- Keep instruments under change control to ensure that the validated state is ensured after changes.

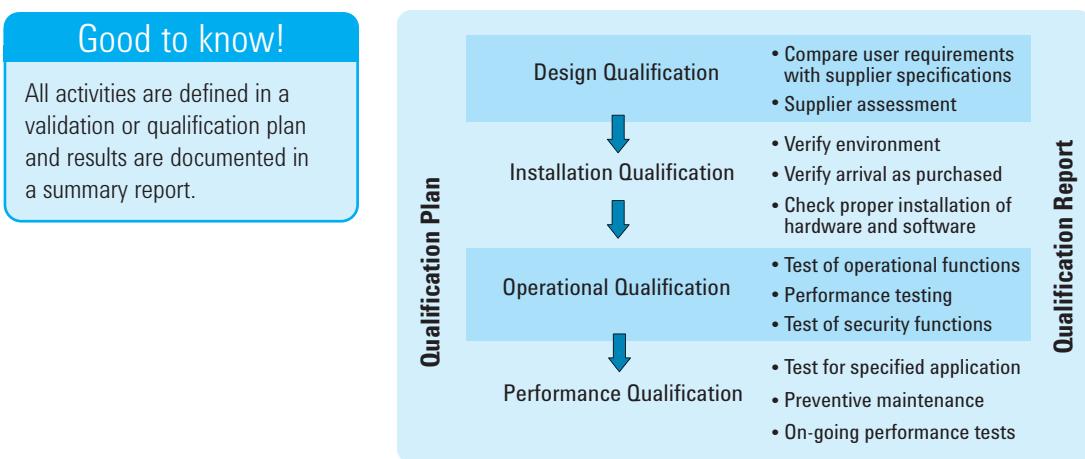
## Chapter 3

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### **Qualification of Analytical Instruments**

## Qualification of Analytical Instruments

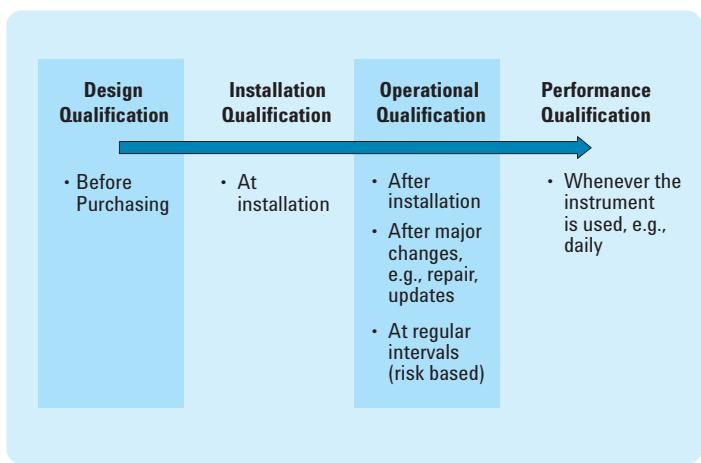
Equipment qualification and validation of computerized systems cover the entire life of a product. It starts when somebody has a need for a specific product and ends when the equipment is retired. For computer systems validation ends when all records on the computer system have been migrated and validated for accuracy and completeness on a new one. Because of the length of time and complexity the process has been broken down into shorter phases, so called lifecycle phases. Several lifecycle models have been described for qualification and validation. Most common ones are the V and 4Q model. The V model includes code development and code testing for software, which is important when validation also covers software development. For the purpose of this primer, where we deal with commercially available instruments and systems, we have selected the 4Q model with phases such as design qualification (DQ), installation qualification (IQ), operational qualification (OQ), performance qualification (PQ). The process is illustrated in figure 2.



**Figure 2**  
**Qualification phases – 4Q model.**

In the DQ phase user requirements are compared with the vendor's specification. In addition, users conduct an assessment of the vendor. In the installation qualification the selected user's environment is checked whether it meets the vendor's environmental specifications. The instrument

is installed according to vendor's recommendations and correct installation is verified and documented. Operational qualification checks if the instrument conforms to the functional specifications, as defined in the DQ phase. Performance qualification verifies that the complete system works for selected applications. Preventive maintenance activities and controlled changes also are part of this phase. All activities are defined in a validation or qualification plan and results are documented in a summary report. Figure 3 illustrates the timeline for the four qualifications.



**Figure 3**  
**Qualification time line.**

### 3.1 Qualification Planning

Qualification activities should be described in a master plan. The plan documents a company's approach for specific activities, for example, how to qualify analytical instruments, how to assess vendors or what to test for commercial computer systems. A master plan serves two purposes: when implemented right, it ensures consistent and efficient implementation of equipment qualifications, and it answers an inspector's question for a company's approach for instrument qualification and system validation. A validation master plan is also officially required by Annex 15<sup>22</sup> to the

European GMP directive: "All validation activities should be planned. The key elements of a validation program should be clearly defined and documented in a Validation Master Plan (VMP) or equivalent documents". FDA regulations and guidelines do not specifically require a validation master plan. However, inspectors want to know what the company's approach towards validation is. The qualification master plan is an ideal tool to communicate this approach both internally and to inspectors. In case there are any questions as to why things have been done or not done, the master plan should provide the answers.

### Good to know!

A validation master plan is officially required by Annex 15 to the European GMP directive.

#### **Within an organization a validation master plan can be developed for:**

- the entire company at a corporate level
- multiple or single sites
- departments
- system categories

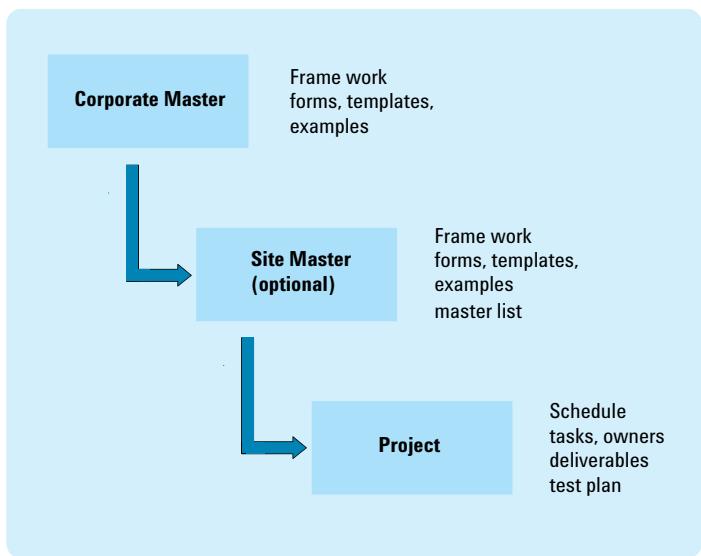
The master plan is a framework for individual project plans and should be written at the highest level possible. This ensures consistent implementation across an organization.

#### **Equipment and computer validation master plans should include:**

1. Introduction with a scope of the plan, e.g., sites, systems, processes
2. Responsibilities, e.g., user departments, QA, IT
3. Related documents, e.g., risk master plan
4. Products/processes to be validated and/or qualified
5. Qualification/validation approach
6. Risk assessment
7. Steps for equipment qualification and computer system validation with examples on type and extent of testing
8. Vendor assessment
9. Handling existing systems
10. Change Control procedures and templates
11. Instrument obsolescence and removal
12. Training plans (system operation, GMP)
13. Templates and references to SOPs
14. Glossary

For each individual project a validation project plan should be developed. This plan is derived from the validation master plan.

Figure 4 shows the link between the master plan and project plan. Ideally master plans are developed at a corporate level. Project plans are written in departments specifically for an instrument or system. Depending on the size, structure and geographic distribution there also may be a site or country specific master plan that is derived from the corporate master plan but has been customized according to specific circumstances and requirements of that site.



**Figure 4**  
Link between master plan and project plan.

The project plan outlines what is to be done in order to get a specific system into compliance. For inspectors it is a first indication of the control a laboratory has over a specific instrument or system and it also gives a first impression of the qualification quality.

For simple equipment qualification a template in table form can be used to outline planned activities. A template example is shown in Figure 5. The left column can be the same for all instruments in the same category, which makes the whole qualification process very efficient.

Scope of the Plan	
Product Description	
Validation Strategy	
Responsibilities	
Supplier Assessment	
Risk Assessment	
Testing Strategies	
DQ	
IQ	
OQ	
PQ	
Traceability Matrix	
Procedures	
Documentation Control	
Approval	

**Figure 5**  
**Template for instrument qualification project plan.**

### 3.2 Design Qualification

“Design qualification (DQ) is the documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument”<sup>2</sup>.

Design qualification is a shared responsibility between the vendor and the user of an instrument.

**The vendor's responsibilities are to:**

- Design, develop and manufacture instruments in a quality control environment.
- Develop functional and operational product specifications.
- Provide information on how software and instruments are validated during development and supported during the entire life of the products.
- Allow user audits, if required, and share approaches for development and testing.

**The user's responsibilities are to:**

- Describe the analysis problem and selection of the technique.
- Describe the intended use of the equipment.
- Describe the intended environment (including computer environment).
- Select and document the functional and performance specifications (technical, environmental, safety).
- Select and assess the vendor.

**Specifications**

DQ should ensure that instruments have all the necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet business requirements. Errors in DQ can have a tremendous technical and business impact, and therefore a sufficient amount of time and resources should be invested in the DQ phase. For example, setting wrong operational specifications for an HPLC system can substantially increase the workload for OQ testing, and selecting a vendor with insufficient support capability can decrease instrument up-time with a negative business impact.

Figure 6 shows a template that can be used to document design qualification. User requirements for an HPLC system should not only have a section to define chromatographic functions and performance but also for physical requirements, construction and vendor requirements to the vendor. A physical requirement could be that all modules should have the same dimensions to allow stackability for optimal use of the lab's bench

Function/ Performance	User Requirements	Supplier Specification	Pass/Fail
<b>Function 1</b>			
<b>Function 2</b>			
<b>Physical Requirements</b>			
<b>Construction Requirements</b>			
<b>Vendor Requirements</b>			

**Figure 6**  
**Template for design qualification.**

space. An example of a construction requirement are accessibility of the detector lamp and flow cell from the front of the instrument for easy maintenance.

Figure 7 shows an example of selected functional and performance specifications of an HPLC system. The user defines his/her requirement specifications and compares them with the vendor's specifications. To set the functional and performance specifications, the vendor's specification sheets can be used as guidelines. However, it is not recommended to simply copy the vendor's specifications, because compliance to the functional and performance specifications must be verified later in the process during operational qualification and also when re-qualifying the instrument at a later time. Specifying too many functions and setting the values too stringently will significantly increase the workload for OQ. For example, if a company has a need for an isocratic HPLC system, but plans to purchase a gradient system for future use, only an isocratic system should be formally specified for regulatory purposes. This means, as long as the instrument is not used for gradient runs no gradient test need to be conducted. Later on, when the system is used for gradient analysis, the specifications should be changed through a change control procedure.

The specifications should be set so that there is a high likelihood that the instrument conforms to them, not only during initial OQ but also during requalification, for example, a year later. Otherwise users may be expected

Function/ Performance	User Requirement	Vendor Specification	Pass/Fail
<b>Autosampler capacity</b>	>90 x 2 mL vials	100 x 2 mL vials	passed
<b>Injection volume precision</b>	<1 % with 10 µL injection volume	<0.5 % with 10 µL injection volume	passed
<b>Flow rate range</b>	1-5 mL/min	0.1-10 mL/min	passed
<b>Baseline noise</b>	<± 2 x 10 <sup>-5</sup> AU	<± 4 x 10 <sup>-6</sup>	passed
<b>Keyboard control</b>	Control through local user interface	Control through local user interface	passed

**Figure 7**  
**Selected HPLC specifications for design qualification.**

to initiate an investigation to determine if the non-qualified instrument could have had a negative impact on the quality of the product. For example, these possibilities are expressed in ICH Q7A<sup>19</sup>:

“Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration”.

## Good to know!

Vendors of critical analytical instruments should be qualified through a formal process.

## Vendor Assessment

Vendors of analytical instruments should be qualified through a formal process. The objective is to ensure that vendors provide high quality products and can give adequate support. For basic equipment, such as pH-meters or a balance, this can be a single page statement describing why the vendor XY has been selected. Certification for a recognized quality system is sufficient for simple instruments. The formal assessment statement should be supported by the quality systems certificate. Figure 8 shows a template with examples to document vendor assessment criteria for analytical instruments.

Requirements	Results	Passed
A Leader in the Market Place		<input type="checkbox"/> yes <input type="checkbox"/> no
Good Experience with the Vendor		<input type="checkbox"/> yes <input type="checkbox"/> no
<b>Quality Assurance</b>		
ISO Certification		<input type="checkbox"/> yes <input type="checkbox"/> no
Documented Software Development		<input type="checkbox"/> yes <input type="checkbox"/> no
<b>Support</b>		
Provide Specifications List		<input type="checkbox"/> yes <input type="checkbox"/> no
Installation Service		<input type="checkbox"/> yes <input type="checkbox"/> no
IQ/OQ Services		<input type="checkbox"/> yes <input type="checkbox"/> no
Phone and Onsite Support		<input type="checkbox"/> yes <input type="checkbox"/> no

**Figure 8**  
**Selected criteria for vendor assessment.**

For more complex systems especially for critical computer systems such as chromatographic data systems a more detailed assessment is recommended. Depending on the complexity and criticality of the system this can be a mail audit, 3<sup>rd</sup> party audit and a direct audit through the user firm.

The purpose of the vendor assessment is to ensure that products are designed, developed and manufactured in a documented quality environment. The assessment should also verify that the vendor provides the right services and can maintain the instrument through phone and on-site support.

### 3.3 Installation Qualification

“Installation qualification (IQ) is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, is properly installed in the selected environment, and that this environment is suitable for the instrument”<sup>2</sup>.

## Good to know!

Responsibility for IQ lies with the user but activities should be supported and can be carried out by the vendor.

Responsibility for IQ lies with the user but activities should be supported and can be carried out by the vendor. For example, before the instrument arrives, the vendor should provide the user with environmental specifications so that the user can prepare the installation site accordingly.

### Tasks performed for IQ include:

- Prepare the laboratory facility according to vendor environmental specifications.
- Control and record environmental conditions, if critical. For example, temperature and humidity.
- Compare equipment received with the purchase order (including, accessories and spare parts).
- Check equipment for any damage.
- Verify that the instrument conforms with physical and construction requirements, as specified by the user.
- Check documentation for completeness (operating manuals, maintenance instructions, standard operating procedures for testing, safety and validation certificates).
- Install hardware (instrument, fittings and tubing for fluid connections, columns in HPLC and GC, power cables, data flow and instrument control cables).
- Switch on the instruments and ensure that all modules power up and perform an electronic self-test.
- List equipment manuals and SOPs.
- Record firmware revision.
- Prepare an installation report.
- Enter instrument data into an inventory data base.
- Prepare, review and sign formal IQ documentation.

## Good to know!

Agilent Technologies provides documentation and services for installation qualification.

Figure 9 shows a template with selected examples that can be used to document completeness of shipment. Figure 10 shows an example of how to check if construction requirements such as stackability and accessibility of flow cells are met.

Purchase Order Item	Complete yes/no, Comment
UV Detector	
10 µL Flow Cell	

Manual Item	Complete yes/no, Comment
Operating Manual	yes
Lamp	yes
Power Cord	yes
LAN Cable	yes
2 x Tubings with Fittings	yes

**Figure 9**  
Template and examples to document completeness of shipment for IQ.

Requirement	Expected Result	Pass/Fail
Accessibility of flow cell and lamp from front	Flow cell and lamp must be accessible from front	Pass
Detector must be stackable with other 1200 Series HPLC modules	All modules have the same width and depth	Pass

**Figure 10**  
Verification of construction requirements for IQ.

All instruments should be entered into the IQ protocol and/or into a database. An example of this documentation is shown in figure 11. The IQ documents should be updated whenever there is a change made to any entry in the IQ documents. Examples of changes are a firmware revision and the location of the instrument within a building or site.

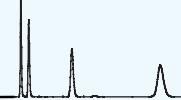
Identification	
Manufacturer	Best HPLC
Model	D4424A
Firmware revision	1.00
Serial Number	E4431A
Internal ID (Asset number)	D33243
Current location	Glab4
Size (w x b x h) (cm)	30 x 22 x 7
Condition when installed	New
Supplier contact phone for services	1+541-64532

**Figure 11**  
**Equipment documentation for IQ.**

### Testing for Installation Qualification

Installation should verify that the instrument hardware and software are properly installed. It does not verify that the instrument conforms to the functional and performance specification. This is done later in the OQ phase. For individual modules, testing is limited to perform and document the instruments self diagnostics when it is switched on.

For systems comprised of multiple modules, correct connection between the modules should be verified. For a modular analytical system, this can be easily achieved by running a test sample and comparing the output with a reference plot. An example of test specifications and results are shown in figure 12.

Actions	Expected Result	Pass/Fail
<p>1) Set instrument conditions according to the installation manual for analyzing the installation verification sample</p> <p>2) Inject the installation verification sample</p>	<p>A chromatogram similar as in the installation manual is obtained.</p> 	<p>1) pass 2) pass 3) pass</p>

**Figure 12**  
**Verification of correct system installation for IQ.**

### 3.4 Operational Qualification (OQ)

“Operational qualification (OQ) is the documented collection of activities necessary to demonstrate that an instrument will function according to its operational specification in the selected environment”<sup>2</sup> Emphasis should be placed on “in the selected environment”. Testing of instrument hardware at the user’s site is required because instrument characteristics can change when shipped from the vendor to the user, for example through mechanical vibration.

#### Good to know!

Users, or their qualified designees, should perform OQ tests to verify that the instrument meets manufacturer or users specification in the user’s environment (USP <1058>).

The most frequently asked questions related to OQ testing are: what should be tested, which are the acceptance criteria, and who should perform the tests? USP answers all the questions in a single sentence: “Users, or their qualified designees, should perform these tests to verify that the instrument meets manufacturer or user specifications in the user’s environment. Designees could be, for example, vendor representatives.”

If a system is comprised of several modules, it is recommended to perform system tests (holistic testing), rather than performing tests module by module (modular testing). Individual module tests should be performed

### Good to know!

If a laboratory uses the same type of instruments from different vendors, it is more efficient to use the same test procedures for all instruments than to use different ones for different vendor instruments.

as part of the diagnosis if the system fails. USP does not give a detailed answer on what exactly should be tested: "The extent of testing that an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter".

Our recommendation is to look at the vendor's test procedures as a starting point and to only make adjustments if there is a specific reason. If a laboratory uses the same type of instruments from different vendors, it is more efficient to use the same test procedures for all instruments than to use different ones for different vendor instruments. We also recommend using the same test procedure for a specific instrument throughout the company, independent from the location. This allows comparing instrument performance across the company and facilitates exchange of instruments and analytical methods.

The frequency of OQ depends on the type of instrument, on the stability of the performance characteristics, but also on the specified acceptance criteria. In general, the time intervals should be selected so that the probability is high that all parameters are still within the operational specifications. Otherwise, analytical results obtained with that particular instrument are questionable. Here the importance of proper selection of the procedures and acceptance limits becomes very apparent. For example, if the baseline noise of a UV/Visible detector is set to the lowest possible limit as specified by the vendor, the lamp will have to be changed more frequently than when set at a factor of 5 higher.

Inspectors expect OQ tests to be quantitative. This means that the test protocol should include expected results and actual results. Figure 13 includes an example for recording of test results of a balance. The header includes three control weights and acceptable limits for the weight. The daily protocol records actual weights and the name and signature of the test person.

Instrument	BestBalance																																														
Serial number	55235A																																														
Maximal weight	110 g																																														
Control weight 1	10,000 mg			Limit: $\pm 10$ mg																																											
Control weight 2	1,000 mg			Limit: $\pm 1$ mg																																											
Control weight 3	100 mg			Limit: $\pm 0.1$ mg																																											
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Date</th> <th>Weight 1</th> <th>Weight 2</th> <th>Weight 3</th> <th>o.k.</th> <th>Test engineer Name</th> <th>Signature</th> </tr> </thead> <tbody> <tr> <td>2/3/06</td> <td>9999.8</td> <td>999.7</td> <td>100.0</td> <td>yes</td> <td>Hughes</td> <td></td> </tr> <tr><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>						Date	Weight 1	Weight 2	Weight 3	o.k.	Test engineer Name	Signature	2/3/06	9999.8	999.7	100.0	yes	Hughes																													
Date	Weight 1	Weight 2	Weight 3	o.k.	Test engineer Name	Signature																																									
2/3/06	9999.8	999.7	100.0	yes	Hughes																																										

**Figure 13**  
**QQ test example.**

### 3.5 Performance Qualification

#### Good to know!

Important for consistent instrument performance are regular preventive maintenance, making changes to a system in a controlled manner and regular testing.

“Performance qualification (PQ) is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use.”<sup>2</sup>

Here emphasis is placed on the word ‘consistently’. Important for consistent instrument performance are regular preventive maintenance, making changes to a system in a controlled manner and regular testing. The PQ test frequency is much higher than for OQ. Another difference is that PQ should always be performed under conditions that are similar to routine sample analysis. For a chromatograph system this means using the same column, the same analysis conditions and the same or similar test compounds.

PQ should be performed on a daily basis or whenever the instrument is used. The test frequency depends on the criticality of the tests, on the

ruggedness of the instrument and on everything in the system that may contribute to the reliability of analysis results. For a liquid chromatograph, this may be the chromatographic column or a detector's lamp.

### Good to know!

PQ testing can mean system suitability testing or the analysis of quality control samples.

In practice, PQ testing can mean system suitability testing or the analysis of quality control samples. This is supported by USP <1058>: "Some system suitability tests or quality control checks that are performed concurrently with the test samples can be used to demonstrate that an instrument is performing suitably." For system suitability testing critical system performance characteristics are measured and compared with documented, preset limits. For example, a well characterized standard can be injected 5 or 6 times and the standard deviation of amounts is then compared with a predefined value. If the limit of detection and/or quantitation is critical, the lamp's intensity profile or the baseline noise should be tested. For chromatographic equipment SST tests are recommended in USP chapter <621><sup>23</sup>.

For ongoing quality control checks samples with known amounts are interspersed among actual samples at intervals determined by the total number of samples, the stability of the system and the specified precision. The advantage of this procedure is that quantitative system performance is measured more or less concurrently with sample analyses under conditions that are very close to the actual application. Figure 14 shows a template with examples for a PQ test protocol.

Test	Test Case	Expected Result	Actual Result	Pass/Fail
Baseline Noise	T10	$<0.5 \times 10^{-4}$ AU	$<0.5 \times 10^{-5}$ AU	Pass
Resolution between Compound A and B	T11	>2.0		
Tailing factor	T12	<1.3		
Precision of Amount Compound A, 6 Replicate Injections	T13	<1%		
Precision of Amount Compound B, 6 Replicate Injections	T14	<1%		

**Figure 14**  
Documentation of PQ tests.

### (Preventive) Maintenance and Repair

Analytical instruments should be well maintained to ensure proper ongoing performance. Procedures should be in place for regular preventive maintenance of hardware to detect and fix problems before they can have a negative impact on analytical data. The procedure should describe:

- The maintenance to be done.
- When it is to be done.
- What should be re-qualified after maintenance is done. For example, a PQ test should always be performed after instrument maintenance.
- How to document maintenance activities.

Instruments should be labeled with the dates of the last and next scheduled maintenance.

Planned maintenance activities should follow a documented instrument maintenance plan. Some vendors offer maintenance contracts with services for preventive maintenance at scheduled time intervals. A set of diagnostic procedures is performed and critical parts are replaced to ensure ongoing reliable system uptime.

Unplanned activities that are necessary in addition to the planned activities should be formally requested by the user of the instrument or by the person who is responsible for the instrument. An example of a request form is shown in figure 15.

Equipment Owner:			
System ID:			
Location of Equipment:			
Requester:			
Date:			
Reason for Maintenance: Describe Observation			
Priority:	High <input type="checkbox"/>	Medium <input type="checkbox"/>	Low <input type="checkbox"/>
Comment:			

**Figure 15**  
**Request form for unplanned maintenance.**

The reason for the requested maintenance should be entered as well as a priority. All maintenance activities should be documented in the instrument's logbook. A template with examples is shown in figure 16.

Log ID	Date	Type of Maintenance	Person Performing Maintenance	Instrument Owner	Comment
	From _____ To	E.g., routine/ non routine	Printed Name _____ Signature	Printed Name _____ Signature	E.g., recalibrated
	From _____ To		Printed Name _____ Signature	Printed Name _____ Signature	

## Good to know!

Defective instruments should be either removed from the laboratory or clearly labeled as being defective.

**Figure 16**  
Maintenance logs.

Defective instruments should be either removed from the laboratory area or clearly labeled as being defective. Procedures should be available for most common problems such as defective UV detector lamps. Procedures should also include information if and what type of requalification is required. Uncommon problems, for example, if an HPLC pump becomes defect without any obvious reason, should be handled through a special procedure that guides users of instruments through the repair process and reinstallation. In this case the impact of the failure on previously generated data should be evaluated.

## Change Control

Analytical instruments and systems go through many changes during their lifetime. New hardware modules may be added to enhance functionality, for example, an automated sampling system replaces a manual one for unattended operation. Vendors may change the firmware to a new revision to remove software errors or application software may be upgraded to be

compatible with a new operating system. Or a complete system is moved to a newly designed laboratory. Some changes are also initiated when new technologies are introduced, for example, a standard HPLC pump is replaced by a rapid resolution pump for higher sample throughput.

Any changes to instrument hardware, firmware and software should follow written procedures and be documented. Requests for changes should be submitted by users and authorized by the user's supervisor or department manager and by QA. Before any change request is approved, business benefits should be compared with the risks a change may bring. USP chapter <1058> states: "Implementing changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required".

USP also recommends following the same 4Q model for changes as for initial qualifications. This means:

- Specifications should be updated, for example in case a new automated sampling system replaces a manual one.
- IQ documents should be updated, if a new firmware revision is installed. Installation documents should also be updated when a system is moved to a new laboratory.
- OQ documents with new test cases and test protocols should be added if the software is upgraded with new functionality and,
- PQ tests need to be updated to verify ongoing system suitability of a new rapid resolution HPLC pump.

Before any change is approved and implemented a thorough evaluation should be made if OQ tests should be repeated. Depending on the change, an instrument may need no, partial or full testing of a system.

### Good to know!

Any changes to instrument hardware, firmware and software should follow written procedures and be documented.

## Chapter 4

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### **Validation of Software and Computer Systems**

## Validation of Software and Computer Systems

### Good to know!

When hardware is qualified at the user's site, the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed (USP <1058>).

Validation of software and computer systems follows the same principle as the qualification of instrument hardware. USP <1058> has a short chapter on software validation. Software is divided into three categories

1. Firmware integrated as chips into instrument hardware for control through local user interface.
2. Software for instrument control, data acquisition, and data processing. An example would be a chromatography data system.
3. Standalone software, for example a Laboratory Information Management System (LIMS) package.

Most valuable is the statement about firmware: "Firmware is considered as a component of hardware of the instrument itself. Indeed the qualification of hardware is not possible without operating its firmware. Thus when the hardware is qualified at the user's site, the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed." The chapter further recommends recording the firmware version as part of IQ and keeping it under change control.

For software categories two and three the chapter refers to the 4Q activities and recommends the FDA guide on software validation for more detail<sup>7</sup>.

In general, the effort to validate a computer system is higher than for instrument hardware. Depending on what it is, the costs for software validation and computer system validation can be 50% or more of the costs for the software itself, with an increasing trend. The main reason is that software offers more and more functionality. All software functions with high impact on drug or API quality should be validated. This does not mean correct functionality should always be tested in the user's laboratory, but as a minimum, all functions should be specified and the need for testing should be evaluated.

This chapter will go into more detail on what is important for validation of software and computer systems. We will follow the same 4Q Lifecycle model as for instrument hardware. The main focus is on relatively small and less complex software and computer systems. As a model we will use a chromatographic data system (CDS) with no or little customization. For more complex systems, for systems with high level of customization and for any software development activities, we refer to literature references with more detail, for example, references 7-12.

## 4.1 Master and Project Planning

### Good to know!

Risk categories should have been determined following a documented process and should be justified.

Software and computer system validation should be well planned. A computer system validation master plan should not only describe validation approaches but should also have an appendix with a list of all computer systems used in a laboratory. Typically, inspectors ask for a list when inspecting data that have been generated by a computer system. The list should uniquely identify all computer systems. It should include a short description of the system and information on the location, the application and whether the system is used in regulated areas. Inspectors also will ask for the risk category of the system. The risk categories can be, for example, high, medium or low. The categories should have been determined following a documented process and should be justified. Criteria are complexity and impact of the system on (drug) product quality. Most likely the inspector will focus during the inspection on systems that have been classified as high risk.

Figure 17 shows a template with examples on how to document a computer system inventory. The list should also include information on the state of validation. Non-validated systems should have a timeframe for system validation. Now the importance of the risk category becomes obvious: Non-validated systems classified as high risk must not be used for any regulated work.

ID/ Asset Number	Description	Location	Application	GxP	Risk h,m,l	Contact	Time Frame for Validation
RV3212	Document Management System	G4 West1	Training Tracking	Yes	m	Bill Hinch TN 432 123	Jan – April 2009

h = high risk, m = medium risk, l = low risk

**Figure 17**  
Template for computer system inventory.

The content items of project plans for computer systems are similar to equipment hardware. However, because of a higher complexity and higher validation effort, the document is longer. For practical reasons table

templates will not work well. Longer project plans are written in text form and a hyperlinked table of contents will help to find individual sections. Project plans should have a section on risk assessment. It should describe how risk assessment is planned and documented and what risk levels mean for the extent of validation.

## 4.2 Requirement Specifications

### Good to know!

Requirement specifications should be linked to test cases in a traceability matrix.

Requirement specifications of software and computer systems should be linked to test cases in some kind of traceability matrix. This can be a table on its own or the link can be built into the requirements table. A template with examples is shown in figure 18. Each specification should have a unique ID code. Criticality of the function can be defined as high, medium or low. Most important questions to ask are: what happens if the function does not work at all or if it produces wrong results? In the next column the test priority is documented. Criticality plays a major role but also the question as to how the user's environment or the user, for example through a wrong user configuration, can influence correct functioning.

Requirement ID	Requirement	Critical	Test Priority	Test ID
4.1	A single computer should be able to control and acquire data from up to four chromatographs	H	H	21
4.2	Before and during data acquisition the status of the instrument should be continually monitored and updated on the display, along with elapsed run time of the analysis	H	H	22
4.3	The transactions that occur during analysis, including any errors and the instrument conditions at the start and at the end of the analysis, should be recorded in the system's log book	M	L	N/A

**Figure 18**  
Example for requirement specification of a chromatographic data system.

Requirements of a CDS should not only be specified on the ability to run a chromatographic analysis, but also on other requirements that are mainly related to system and data security, and data integrity. Requirements are stated in FDA's regulation for electronic records and signatures: 21 CFR Part 11<sup>21</sup> and in Annex 11 to the European GMPs<sup>24</sup>. Very important is the electronic audit trail function. Selected specifications for audit trail functionality are shown in figure 19.

Requirement ID	Requirement	Critical	Test Priority	Test ID
12.02	Data system should have computer generated, time-stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic record	H	H	6.1
12.03	The system should record individual users who are responsible for creating, modifying and deleting records	H	H	6.2
12.03	It should be possible to view and print audit trail information	H	M	N/A

**Figure 19**  
**Selected specifications for electronic audit trail.**

### 4.3 Vendor Assessment

A thorough vendor assessment is even more important for computer systems than it is for instrument hardware. When instrument hardware arrives in a laboratory it can be physically inspected for any damage and specifications can be fully tested so users can get a good impression of the quality. This is not so easy with software. DVD covers always look very nice but they say nothing about the quality of the product. Also most likely it is impossible for a user to test all functions of a complex commercial computer system. Errors may not even become obvious during initial use, but only later when certain functions are executed together.

During vendor assessment, the user should verify that the software has been designed, developed and validated during and at the end of development. The vendor's capability and practice to support the user before and during installation and as long as the software is used should also be checked.

#	Assessment	Comment
1	Through own experience with the vendor	Experience may come from the product under consideration or from other products. Criteria are: Quality of the products (failure rate). Responsiveness in case of errors (phone call, on-site visit, bug fix).
2	Through references outside the company	Useful if there is no experience with the vendor within your company. Criteria are: Position of the vendor in the market place. Image of the vendor as software supplier. Quality reputation of the product.
3	Checklist – Mail audit	Use checklists available within your company and through public organizations, e.g., PDA and from private authors.
4	Assessment through 3 <sup>rd</sup> party audits	Gives an independent assessment of the quality system and/or product development.
5	Vendor audit through the user firm	Gives a good picture of the vendor's quality system and on the vendors testing practices.

**Figure 20**  
**Methodologies for vendor assessment.**

Figure 20 lists different assessment methodologies. Costs for the assessment increase from 1 to 5. Vendor audits are most expensive but could make sense when a company plans to purchase complex computer systems for multiple laboratories or sites. The final decision on the methodology should be based on risk assessment. Criteria are vendor risk and product risk.

Criteria for product risk are:

- System complexity

- Number of systems to be purchased
- Maturity of the system
- Influence on other systems
- Impact on (drug) product quality
- Impact on business continuity
- Level of customization

When users purchase software such as CDS they need support from a specific vendor for a lengthy time to ensure retrieval and readability of data for several years. Therefore, the future outlook of a company and the ability to support data is important. The way to make an assessment is to look for how long older data can be supported by the current system. This in combination with the size of the company and the position of the company in the target market are good indications to assess the vendor risk. The selection decision for a specific vendor should be justified and documented.

#### 4.4 Installation Qualification

Key points for IQ of computer systems are to verify correct software installation and to document all computer hardware, software and configuration settings as the initial baseline configuration.

Recommended steps for installation of computer systems include:

- Install software on computer following the manufacturer's recommendations.
- Verify correct software installation to make sure that all files are correctly installed. Software with MD5 based checksum routines is a good tool for this.
- Make a back-up of the software.
- Configure peripherals like printers and instrument modules.
- Identify and make a list with a description of all hardware, operating system software and application software. Identification of software should include the version number.
- Make system drawings, where appropriate.
- For networked systems: check communication with network devices.

As part of the installation process computer systems should be well documented with:

- Computer hardware, e.g., manufacturer, model.
- Computer firmware, e.g., revision number.
- Operating system: vendor, product identifier and version.
- Application software: vendor, product identifier and version.
- Hardware peripherals, e.g., printers, CD-ROMs.
- Network hardware, firmware, software and cables.
- Documentation, e.g., operating manuals and specifications.

<b>Verify Completeness of Shipment</b>	
Software	<input type="checkbox"/> yes <input type="checkbox"/> no
Operation manuals	<input type="checkbox"/> yes <input type="checkbox"/> no
<b>Verify correct software installation</b>	
<b>Document system items</b>	
Computer	
Monitor	
Printer(s)	
Other peripherals	
Chromatography software	
Other software	

**Figure 21**  
**Computer system documentation for IQ.**

Information should be entered into a data base and should be readily available when contacting vendors to report a problem during operation. Figure 21 shows a template with examples of an installation protocol.

#### 4.5 Operational Qualification

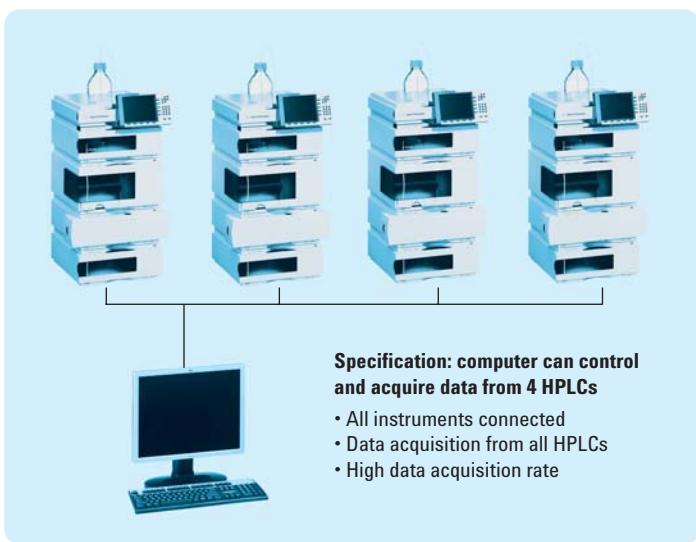
Testing software and computer systems can be a complex task. Extent of testing should be based on a justified and documented risk assessment. The required effort mainly depends on:

- the criticality of the system for (drug) product quality and data integrity
- the complexity of the system
- information on what has been tested by the vendor and the related test environment
- the level of customization and configuration.

### Good to know!

Specific user configurations should be documented and tested.

Most extensive tests are necessary if the system has been developed for a specific user. In this case the user should test all functions. For commercial off-the-shelf systems that come with a validation certificate, only tests should be done of functions that are highly critical for the operation or that can be influenced by the environment. Examples are data acquisition over relatively long distances from analytical instruments at high acquisition rates. Specific user configurations should be documented and tested, for example, correct settings of network IP addresses should be verified through connectivity testing.



**Figure 22**  
Example for high load testing.

When computer systems can control and obtain data from multiple analytical instruments, tests should be conducted with a high number of instruments transmitting data. The example in figure 22 illustrates that, according to specifications, 4 instruments can be controlled. Correct functioning of the system should be verified with all four instruments connected and delivering data at high acquisition rates.

Test ID: _____	Test System ID: _____				
Test Objective: _____	Specification: _____				
<b>Step</b>	<b>Test Procedure</b>	<b>Expected Result</b>	<b>Actual Result</b>	<b>Required Documents</b>	<b>Pass/fail</b>
1					
2					

**Tester: I confirm that I have all tests executed as described**  
 Name: \_\_\_\_\_ Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
 Tests passed:  yes  no Comment: \_\_\_\_\_

**Reviewer: I confirm that I have reviewed test documentation**  
 Name: \_\_\_\_\_ Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**Figure 23**  
**Template for testing.**

Test results should be formally documented. Figure 23 shows a template and examples for a test protocol. It consists of three parts. The header describes the test system, test objective and the specification. The step-by-step test procedure, expected results and actual results are documented in the middle. The test protocol also has a column to document evidence of testing. This can be a print out, a screen capture or just handwritten recording of visual observations. The lower part documents the names of the test engineer and reviewer and has a signature section.

## 4.6 Performance Qualification

### Good to know!

PQ tests should be designed to challenge a complete system's performance.

PQ should be designed to challenge a complete system's performance. For a computerized analytical system this can mean, for example, running system suitability testing, where critical key system performance characteristics are measured and compared with documented, preset limits.

PQ activities for CDS can include:

- A complete system test to prove that the application works as intended. This can mean running a system suitability test or analyzing a well characterized sample through the system and comparing the results with results previously obtained.
- Regression testing: reprocessing data files and comparing the results with previous results.
- Regular removal of temporary files.
- Regular virus scan.
- Auditing computer systems.

Most efficient is to use software for automated regression testing. The software runs typical data sets through a series of applications and calculates and stores the final result using processing parameters as defined by the user. During regression testing the data are processed again and results are compared with previously recorded results. Normally these tests don't take more than five minutes, but give assurance that the key functions of the system work as intended.

## 4.7 Configuration Management and Change Control

The purpose of configuration management is to be aware of the lifetime composition of the system from planning to retirement. The initial or baseline configuration of a system has been documented as part of IQ.

Any changes to specifications, programming codes or the initial set up of computer hardware should follow written change control procedures and be documented. Changes may be initiated because errors have been found in the program or because additional or different software functions or hardware may be desirable. Requests for changes should be submitted by users and authorized by the user's supervisor or department manager.

<b>Form ID</b>	Change ID	Item ID	
<b>Initiator</b>	Date	Location	
<b>Description of Change</b>	<i>(Include Reason for Change)</i>		
<b>Priority</b>	<input type="checkbox"/> high <input type="checkbox"/> medium <input type="checkbox"/> low		
<b>Impact Assessment</b>	<i>(Business, Technical, Validation)</i>		
<b>Risk Assessment</b>	Risk, Likelihood, Severity, Recovery		
<b>Regulatory Notification required?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No		
<b>Test Plan</b>			
<b>Roll Back Plan</b>	<i>(In Case of Severe Problems)</i>		
<b>Change Approval</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No Comments		
<b>Approved by</b>	Name	Signature	Date

**Figure 24**  
**Example for change request form.**

Figure 24 shows a form that can be used to request changes. The form should include information on the priority and on business benefits versus costs for additional validation tasks. This information is important to assess if the change has a business advantage and should be approved or rejected.

The form should also include information about whether regulatory notification is required and the roll back plan. A roll back plan is like a contingency plan that becomes effective when a change introduces an error, which causes the system to fail. The roll back plan ensures that the system can be brought back to the last working system configuration.

## 4.8 Validation Report

### Good to know!

The validation report should be organized in such a way that it has all the elements and follows the outline of the validation plan.

At the end of validation, a summary report should be developed. This should be a mirror of the validation project plan. It should be organized in such a way that it has all the elements and follows the outline of the validation plan. This makes it easy to check if all plan items have been completed successfully. Deviations should be documented, if there are any, together with corrective actions and/or work around solutions. The report should include a statement that the instrument or system is qualified or validated. After the statement and the report have been signed by management, the product can be released for operation.

Typically, the validation plan and the report are the first documents inspectors want to see when they inspect a validation project. If everything is well organized and documented, it may well be that after looking at both documents inspectors get such a good impression about the validation work that they will focus on other inspection areas.

## 4.9 Validation of Existing/Legacy Systems

It frequently happens that existing instruments and systems are not formally validated if they are not used in a regulated environment. Sometimes these systems are called legacy systems. They should be validated if they will be used in a regulated environment, a process called retrospective validation. Inspectors expect the same documented evidence that the system is suitable for its intended use as for new systems.

We recommend following the same 4Q model for validation as for new systems. The main difference is in the DQ phase. Most likely there is not much information from the vendor available and vendors cannot be assessed. There is also no need to develop requirement specifications from scratch. The big advantage of an existing system is that there is a lot of information from past use and the used functions are well known.

The most important task for an existing system is to document the system functions used along with any comments about problems with the functions. The system should be fully documented for IQ, like a new system.

OQ and PQ testing should focus on functions that caused problems in the past. After successful OQ and PQ testing, a summary report should be developed and signed by management. This means the system can be released for use in a regulated environment.

## 4.10 Validation of Spreadsheet Applications

Spreadsheets are widely used in laboratories for data capture, data evaluation and report generation. For example, they can be used to correlate data from a single sample analyzed on different instruments and to obtain long-term statistical information for a single sample type. The processes may be automated, for example, enabling the analytical data to be transferred, evaluated and reported automatically. In all of these programs, analytical data are converted using mathematical formulae.

Today the understanding is that the programs themselves don't have to be validated by the user, e.g. MS Excel. What should be validated are the custom calculations and program steps written by the laboratory. There should be some documentation on what the application program, written by the user as an add on to the core software, is supposed to do, who defined and entered the formulae and what the formulae are.

Development and validation of spreadsheets should follow a standard operating procedure. Recommended steps are:

- A user drafts a proposal for a new spreadsheet. The proposal should include a description of the problem that the spreadsheet should solve, how it is handled now and how the spreadsheet can improve efficiency.
- The system owner writes a project plan.
- The system owner collects inputs from anticipated users on requirement specifications and writes requirement specifications.
- The programmer defines and documents required functions. Functions are reviewed by users.
- The programmer develops design specifications, for example, which formulas are used and the location of input/output cells. For complex spreadsheets and for spreadsheets with VBA scripts, the design specifications are reviewed by peers of the programmer.
- The programmer develops the worksheet and creates functional tests. The code is reviewed by peers of the programmer (structural testing) for spreadsheets with VBA scripts.
- The programmer writes a user manual.
- The system owner develops a test protocol for users.
- Users load the spreadsheet onto their computer.
- Users test the spreadsheet and document the results.

## Chapter 5

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### **Implementing USP Chapter <1058>**

## Implementing USP Chapter <1058>

USP <1058> is the authoritative guide for analytical instrument qualification. Even though as a chapter with a number above 1000, generally, it is not mandated and alternative approaches are possible. Nevertheless, we would recommend implementing it for FDA regulated environments because of several reasons.

- The chapter is mandated if any USP monographs require using qualified instruments for a specific analysis.
- FDA inspectors expect instruments to be qualified when used for regulated testing.
- The applied 4Q qualification model has been very well established since over 10 years and many laboratories are familiar with it.
- The model is applicable to all types of instruments ranging from simple devices to complex systems.
- The model is flexible and allows laboratories to define test procedures and acceptance criteria according to the instrument's intended use.

Because of the importance of the chapter and its advantages we want to dedicate this last primer chapter to recommendations for implementation of USP <1058>.

### 5.1 <1058> Instrument Groups

Analytical laboratories typically include a set of tools ranging from simple nitrogen evaporators to complex automated instruments. Depending on the complexity, the qualification efforts vary. The concept is always the same, but the extent of testing and the required amount of documentation will change. For example, a very simple instrument may only need one or two minutes for physical inspection and making a tick mark in a check list, while more complex systems can easily take several days for full validation.

Because of the large variety of instruments, with different qualification and documentation requirements, it can be very complicated if each type of instrument is handled differently. To simplify the process, USP recommends dividing all instruments into three groups A, B, and C and to define for each group a specific set of qualification tasks.

The standard lists examples for each group but at the same time makes it clear that the categories are not only instrument but also applications specific. Examples for all three groups are shown in figure 25.

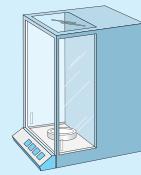
- Three instrument categories: A, B, C
- Level of qualification depends of the type of instrument and on application
- User defines category and level of qualification

**Magnetic Stirrers  
Vortex mixers**



Visual inspection.  
May not require  
formal qualification

**Balances  
pH meters**



Verification with  
specifications

**HPLC systems  
Mass spectrometers**



Full qualification

**Figure 25**  
**Instrument groups A, B, and C.**

Group A includes standard equipment with no measurement capability. Examples are nitrogen evaporators, magnetic stirrers, vortex mixers and centrifuges. Group B includes standard equipment and instruments providing measure values, for example, a balance. This group also includes equipment controlling physical parameters, such temperature, pressure or flow. Examples are water baths and ovens. Group C includes instruments and computerized analytical systems. Examples are computerized IR-spectrometers, HPLCs and mass spectrometers.

## 5.2 Allocating Instrument into Instrument Groups

USP recommends dividing analytical instruments into groups, but does not include a matrix with instruments allocated to groups. On the other hand such a matrix is of utmost importance for a company; otherwise discussions will start over and over again about the right allocation whenever an instrument has to be qualified. Our recommendations are:

- 1) Develop a list with all analytical instruments and allocate all of them into groups A, B or C.
- 2) Develop a list of procedures for each group that should be available and used when qualifying instruments.
- 3) Develop a list of tasks for each group that should be executed when qualifying instruments.

### Good to know!

Within a company the procedures and qualification tasks for instrument groups should be developed at the highest possible level.

Within a company the lists, procedures and tasks for groups A, B, and C should be developed at the highest possible level; and preferably there should only be one set available. Having a harmonized approach reduces subjectivity for qualification and it is not only very efficient but also ensures consistency. We would suggest putting examples of instrument categories and applications in an equipment validation master plan. A harmonized approach is also advantageous for external audits or inspections, especially when several laboratories are inspected by the same inspector in the same time frame.

## 5.3 Procedures and Qualification Protocols for Three Groups

The number of procedures required increases from groups A to C. Each company should have a document that specifies which type of procedures should be developed. A template with examples is shown in Figure 26. The point here is not to exactly follow the examples, and this list does not originate from the USP, but it is very important to have a list available within an organization.

The number of documents increases from A to C. An operating instruction and a procedure for reporting problems are enough for group A devices. Group B requires additional procedures for qualification, change control and preventive maintenance and repair. Additional procedures for group C are specific to computer systems, for example, back-up, security, and system administration.

A	B	C
Operation	Operation	Operation
	Qualification	Qualification
	Change control	Configuration management
		Back-up, restore and archival
		Security
		System administration
	Preventive maintenance & repair	Preventive maintenance & repair
Problem reporting	Problem reporting	Problem reporting
		Periodic review
		Retirement

**Figure 26**  
**Recommended procedures for groups A, B and C.**

A company should also provide information on which qualification steps should be executed. An example is shown in figure 27. Some recommendations are from the USP chapter. For example it states for group A: "The manufacturers specification of basic functionality is accepted as user requirements. Conformance of group A equipment with user requirements may be verified and documented through visual inspection". This means a simple checklist can be enough for documentation.

The difference between B and C are mainly in areas of vendor qualification and risk assessment. For B we only document the vendor's quality system and keep the certificate as a record. For computerized systems in C we should have a vendor assessment program. Risk assessment is also recommended for C. The number of required documents for B and C does not vary much. However, the size of the documents and the format will be different. For example, a qualification plan in B can be documented on a one or two-page template. For C this could be easily a 20 page text document.

A	B	C
	Qualification plan (Table form template)	Qualification plan (Text document)
Vendor specifications	User requirements specification	User requirements specification
		Risk assessment
ISO 9000 certificate	ISO 9000 certificate	Vendor assessment
Checklists used during initial inspection	DQ, IQ	DQ, IQ, configuration baseline
	OQ and PQ tests	OQ and PQ tests
	Maintenance, repair and change logs	Maintenance, repair, back-up and change logs
	Qualification report	Qualification report

**Figure 27**  
**Recommended qualification tasks for groups A, B and C.**

#### **5.4 Responsibilities, Communication and Training**

Implementation of USP <1058> should be communicated to everybody in the organization who is involved in qualification and validation of instruments and systems. People should receive training on the USP chapter, on why the company decided to implement the chapter and what it means for day-to-day operation. The training should be documented and supervisors should follow-up to verify effectiveness.

Vendors should also be informed about implementation of USP and they should be advised to study the chapter and follow-up to fulfill vendor requirements. USP <1058> has a chapter on roles and responsibilities for users, the quality assurance unit and manufacturers.

#### **Users**

Users of analytical equipment have the ultimate responsibility for instrument operations and data quality. It is an FDA GMP requirement that analysts must sign the analytical test result and therefore also have the ultimate responsibility to make sure instruments and computer systems

## Good to know!

Whoever is doing the qualification work should be trained and training certificates should be filed with the qualification documents.

are qualified and validated. Users should be adequately trained in the instrument's use. Training can be provided by anybody who is proven to be competent, for example by vendor representations, 3rd parties and by internal resources.

The fact that users have ultimate responsibilities for instrument qualification does not mean that they have to conduct all qualification activities. For example, IQ and OQ can be delegated to the instrument vendors or to a 3rd party organization. On the other hand PQ should be performed by users because the tests are applications specific and require a good knowledge of the application. Advantage of using vendors for IQ/OQ is that they have all the necessary experience and procedures and even more importantly, they bring along calibrated tools that are required for the qualification. Vendors with worldwide presence typically also offer qualification services around the globe. This is important for companies operating in multinational environments. Whoever is doing the qualification work should be trained and training certificates should be filed with the qualification documents.

## Quality Assurance

The role of the Quality Assurance unit is the same as for any other regulated activity. QA personnel are responsible for assuring that the qualification process meets compliance requirements and conforms to internal procedures. QA personnel should also train or advise user groups on regulations and lead or help with the vendor assessment process.

## Developers, Manufacturers and Vendors

Developers and manufacturers are responsible for the design of the instrument or software program and for providing specifications to the user. They should validate processes used in development and manufacturing as well as during the entire support period. Manufacturers should allow user audits and share validation processes, test procedures and test results with regulated users. Manufacturers and vendors should also notify all users about hardware and software defects discovered after a product's release. Furthermore, manufacturers or vendors should provide user training, installation and qualification support and repair services.

## Agilent Technologies' Commitment to Compliance

Agilent Technologies develops and manufactures hardware and software solutions that offer the most comprehensive built-in compliance capabilities. You can validate these systems, methods and data in the shortest possible time and at very low cost.

Agilent's "five steps to successful validation" procedure for LC, GC, CE separation and detection instrumentation includes:

**Step 1:** Design qualification (DQ)

**Step 2:** Installation qualification (IQ) and operational qualification/performance verification (OQ/PV)

**Step 3:** Method validation

**Step 4:** Performance qualification (PQ)

**Step 5:** Electronic records protection for compliance with 21 CFR Part 11

More information on [www.agilent.com/chem/validation](http://www.agilent.com/chem/validation)

### Additional resources

- Regular e-seminars provide basic and update information on validation and compliance in laboratories.

More information on [www.agilent.com/chem/eseminars](http://www.agilent.com/chem/eseminars)

- To make regulatory compliance even easier, Agilent Technologies offer cost-effective and proven risk-based qualification services that meet evolving business needs. The company has been ranked several times by lab professionals in independent surveys as the preferred supplier for validation!

More information on [www.agilent.com/chem/compliance](http://www.agilent.com/chem/compliance)

- Regular QA/QC newsletter with FDA and other compliance updates

More information on [www.agilent.com/chem/pharmaqaqc](http://www.agilent.com/chem/pharmaqaqc)

More information on Agilent products: [www.agilent.com/chem](http://www.agilent.com/chem)

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## Glossary

CDS	Chromatographic Data System
cGMP	Current Good Manufacturing Practice
CFR	(US) Code of Federal Regulations
DO	Design Qualification
EU	European Union
FDA	Food and Drug Administration
GAMP	Good Automated Manufacturing Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
ICH	International Conference for Harmonization
IQ	Installation Qualification
ISO	International Organization for Standardization
LIMS	Laboratory Information Management System
OECD	Organization for Economic Co-operation and Development
OOS	Out of specification
OQ	Operational Qualification
PASG	(UK) Pharmaceutical Analytical Sciences Group
PIC/S	Pharmaceutical Inspection Cooperation Scheme.
PQ	Performance Qualification
QA	Quality assurance
QC	Quality control
SOP	Standard operating procedure
SST	System suitability testing
USP	United States Pharmacopeia